REMARKS

This is in response to the Office Action dated January 12, 2005. The claims in the case are claims 1, 2, 6, 7, 27 and 31-36. The only outstanding rejection is under 35 U.S.C. §103(a).

The Office Action maintains the rejection under 35 U.S.C. §103(a) as allegedly obvious over U.S. Patent No. 5,804,183 to Filpula ("Filpula") in view of Takaku *et al.* (1995) *Jpn. J. Cancer Res.* 86:840-846 ("Takaku"), Sugimura *et al.* (1992) *Melanoma Res.* 2:191-196 ("Sugimura") and Oyanagi *et al.* (1986) *Tohoku J. Exp. Med.* (Japan) 148(4)385-391 ("Oyanagi").

The Examiner maintains the rejection after frankly admitting that Filpula does not teach a method for identifying a cancer susceptible to AD therapy by detecting the presence or absence of argininosuccinate synthetase (as instantly claimed) by asserting that:

> [I]n view of a clear correlation between the low level of argininosuccinate synthetase (ASS) gene expression in human melanoma cell lines and high sensitivity to AD based on the teaching of Sugimura *et al.*, and in view that not all tumor cells are susceptible to arginine deprivation (AD) therapy, and further in view that cancers such as carcinoma, melanoma or hepatoma that have been successfully treated by arginine deprivation (AD) therapy, as taught by US 5,804,183, Takaku *et al.*, all are deficient in or have reduced level of ASS, as taught by US 5,804,183, Takaku *et al.*, and Oyanagi *et al.*... (Office Action dated January 12, 2005, pp. 3-4).

In order to sustain such a rejection, it must follow that one of skill in the art, in view of the combination of these teachings would be motivated to combine the teachings and have a reasonable expectation of success. The motivation to combine the references cannot come from the applicants' teachings, but must be found in the references themselves or knowledge generally available to one of skill in the art (MPEP § 2143).

First, the art should be evaluated as would have been understood by a person of skill in the art at the time the application was filed. At that time, Takaku was known to have taught that arginine deiminase effectively depleted cells of arginine, not that any cell type is deficient in ASS. As is evident from the Abstract, last sentence, where it is taught that tumor

cell growth inhibition caused by *Mycoplasma arginini* arginine deiminase ("a-AD") "originates from the depletion of the essential nutrient L-arginine...." Takaku does ***not*** teach that tumors were deficient in ASS.

Further, as stated in the Abstract, the addition of L-ornithine, which is biosynthesized from L-arginine, partially restored the growth of the cells. This is likely due to the use of ornithine in polyamine biosynthesis. Takaku also tested the addition of citrulline on the growth of cells in the *absence* of arginine deiminase (see Figure 6) but did not test whether the addition of citrulline restored arginine depletion. In the urea cycle, depicted as Figure 1, one might expect citrulline to be converted to argininosuccinate by ASS and then to arginine by ASS lyase. Takaku appears to rely on the fact that arginine deiminase would effectively raise the level of citrulline in the media (page 844, last paragraph), as arginine deiminase converts arginine to citrulline. By adding citrulline to the media of cells not treated with arginine deiminase, Takaku showed that the inhibitory effect of arginine deiminase was *not* an increased level of citrulline in the media. Takaku never draws the conclusion that the tumor cells of any type may also be deficient in ASS.

As the Examiner correctly notes, Oyanagi describes a patient (Case 2) that died of hepatoma. This patient also was found, at the time of death, to have only a 20% reduction in liver ASS activity (see Abstract). However, a careful examination of Oyanagi reveals that the fact that the patient died of hepatoma does ***not*** indicate that the hepatoma was in any way related to the ASS deficiency.

The patient (Case 2) had the onset of symptoms (unconsciousness) at the age of 27 and histological findings revealed that the patient had *cirrhosis*, and he was placed on a low protein diet since he was diagnosed with adult-type citrullinemia (page 386). However, his liver dysfunction was *progressive* and he died of hepatoma ***4 years later*** (page 386). There is no indication that the patient's hepatoma was the primary cause of citrullinemia or that the hepatoma was sensitive to arginine depletion, or that the hepatoma was deficient in ASS. Nothing in Oyangi teaches or suggests that hepatomas are deficient in ASS or are susceptible to arginine depletion therapy. The patient was placed on a low protein diet due to citrullinemia, not to treat a tumor (which may not even have existed at the time of diagnosis of citrullinemia). Nothing in case study 2 suggests that hepatoma caused the citrullinemia; the hepatoma may have been a subsequent event, brought on by progressive cirrhotic disease.

Underscoring this point, in the final paragraph, Oyanagi speculates that "the cause of citrullinemia in our patients might be the result of an abnormality of the regulatory gene or a disturbance in the translation of mRNA." Thus, it is clear that Oyanagi believed the citrullemia to be genetically based and did not correlate ASS deficiency with any type of cancer, as suggested by the Examiner.

Sugimura teaches that certain melanoma cells which were susceptible to arginine depletion therapy were also deficient in ASS. Notably, *not all the melanoma cells that were susceptible to treatment with arginine deiminase were completely ASS deficient.* One cell line GG361 "exhibited a significant level of ASS gene expression" yet was still sensitive to AD therapy (page 194, first paragraph under "Discussion"). At best, Sugimura teaches that a handful of melanomas which are highly sensitive to AD therapy are also ASS deficient.

This is the context in which Filpula must be understood. Filpula would know that arginine deiminase was useful in treating certain tumors due to its reduction of available arginine, and would work for certain tumors (such as those treated by Sugimura). Filpula's asserted contribution was isolation of arginine deiminase from *Mycoplasma arthriditis* which had more available lysines for modification with conjugates (see Filpula, col. 2, lines 47-54 and col. 3, lines 5-15). Filpula teaches that arginine deiminase polymer conjugates (which reduce arginine in the circulation) may be used to treat a variety of conditions that *are known to respond to AD therapy* (col. 13, lines 6-15). Among the conditions which Filpula teaches are known in the medical arts to be susceptible to AD therapy are certain carcinomas that are deficient in ASS (specifically citing the melanomas described by Sugimura), nitric oxide-related conditions, and certain dietary conditions (*e.g.*, modulating the effects of low protein diets (Filpula, Col. 13, lines 7-27). Filpula teaches only that these categories of conditions *are known to respond to arginine deiminase therapy.* The three conditions are not treated because they have the same underlying mechanism which responds to arginine deprivation. Filpula fails to state that any tumor with ASS deficiency would respond to arginine deiminase therapy. Nowhere does Filpula make that connection and the art of record fails to make up for the deficiency.

Thus, Filpula merely suggests that specific tumors, known to respond to arginine deprivation therapy, would be expected to respond favorably to *Mycoplasma arthriditis*

arginine deiminase conjugate therapy. Filpula does not suggest that ASS deficiency *in and of itself* is predictive of which tumors would respond to arginine deprivation therapy.

Sugimura merely teaches that certain melanoma cells are sensitive to treatment with arginine deiminase and this sensitivity ***may*** be attributable to reduced levels for ASS. Sugimura's finding did not have complete concordance. Melanoma cell line G361 exhibited "a significant level of ASS" but nevertheless was sensitive to arginine deiminase, calling into question whether ASS deficiency *per se* correlates with arginine deiminase sensitivity. As Sugimura did not examine other cell types, a broad interpretation that tumors in general having ASS deficiency would be susceptible to AD therapy would not have been warranted. Moreover, Sugimura did not look at ASS at the protein level, but merely looked at transcription of the ASS gene by RT-PCR. It was not determined whether the apparent reduction in ASS expression affected the amount of ASS protein present. Neither Sugimura nor Filpula interpreted Sugimura's results as broadly as the Office Action. Oyanagi and Takaku add nothing to remedy the deficiency in the teachings of Filpula and Sugimura.

The discovery that one could screen tumor types for ASS protein levels as a predictive indicator of which tumors would be sensitive to AD therapy was recognized by the inventors, not the prior art, and such correlation was not obvious in view of the art of record.

Applicants respectfully submit that the claims are in condition for allowance, which action is respectfully requested.

Respectfully submitted,

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